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09/903,378	07/10/2001	Arthur J. Chirino	A-69566-1/RFT/RMS/RMK	8329

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EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/903,378	Applicant(s) Chirino et al
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 9, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5 and 7-17* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5 and 7-17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Claims

1. Amendment filed 07/09/03 is acknowledged. Claims 1,7,8 are amended. Claim 6 is canceled. Claims 1-5, 7-17 are pending.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, second paragraph.

2. Claim 1-5, 7-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The claims are drawn to modulating protein immunogenecity which is a biological function determined experimentally. The entire claimed method, however, is *in silico*, i.e. all steps are drawn to computer modeling. It remains vague and indefinite, without an experimental testing of functions of candidate variant protein, whether computer modeling steps result in modulation of immunogenecity.

Response to arguments

Examiner maintains that without an experimental testing of functions of candidate variant protein it remains unclear whether and how computer modeling steps result in modulation of immunogenecity. Applicant refers to claim 2 reciting testing candidate protein for its immunogenecity. However, it is not clear how a virtual peptide which has not been synthesized, only modeled on computer, can be tested using experimental *in vitro* methods.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 7-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to modulating of immunogenecity of proteins. There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions on a real protein synthesized following its *in silico* design.

The only mention of "immunogenecity filter" on p. 30 (lines 15-21) is so vague that it is not clear whether applicant was in possession of any algorithm or scoring function that would result in a design of a protein with altered immunogenecity.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cat*h, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that applicants generated any compound which, after computer generation, and application of "computational immunogenecity filters"

had immunogenecity different from that of parent molecule. Similarly to *In re Wilde*r, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denie*d, 469 U.S. 1209 (1985)the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."

Response to arguments

Applicant argues that sufficient physical and/or chemical properties are disclosed. None of these were found in the specification. In regard to functional characteristics applicant correctly states that a sequence can be optimized using computational methods and that numerous known computerized algorithms predict binding of peptides to MHC molecules. Examiner does not dispute whether applicants were in possession of a method of determining binding to MHC molecules, however. At issue is whether applicant was in possession of method of modulating immunogenecity. Discrepancy between predicted data on MHC binding and immunogenecity is well known. Thus, Meister et al. (i.e one of the methods used in the instant method, see p. 33, line 35) discusses that not all peptides predicted to bind to MHC peptides can be expected to stimulate immune response, both *in vivo* and *in vitro*. For example, only about one third (!) of peptides having motif corresponding to a given MHC allele have been found to interact with that MHC molecule. In some cases peptides which bind MHC molecules are immunodominant. See p. 598, second paragraph, and p. 582,

second paragraph. Buus et al teaches that "there are still many examples of erroneous prediction of binding at the individual peptide level; furthermore, interaction at one subsite may affect interactions at other subsites" (see paragraph bridging pages 211-212).

Section 112, first paragraph, requires the patentee to "show that an invention is complete by disclosure of substantially detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the invention. Even if the inventors were reasonably certain that immunogenecity of target protein can be modified using claimed computational methods, there is no showing in the patent that they knew that to be a fact. There is no showing of a single embodiment demonstrating modified immunogenecity. The reader can certainly appreciate the goal but establishing goals does not make a patent. As was mentioned in the rejection, the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). [1]

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[1]Applicant's traverse that the referenced case law addresses DNA rather than protein modeling does not effect written description patentability issues discussed in this rejection.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-5, 7-17 are rejected under 35 U.S.C. 103(a) as obvious over Fleckenstein et al (Eur. J. Biochem., 240, 71-77, 1996) or Abrams (Current Opinions in Immunology, 12, 85-91, 2000; references C15 and C1, respectively) in view of Altuvia et al or Meister et al or Buus et al (references C2, C37, and C9, respectively) and further in view of Mayo et al (WO 98/47089 or US Patent 6,269,312; references B1 and A1, respectively).

The instant claims are drawn to method of modulating immunogenecity of a protein comprising the steps of inputting the protein's structure into a computer, modulating the structure at variable positions, and identifying candidate variant proteins by applying "computational immunogenecity filter". The latter "filter", as explained in specification, p. 30, can be any of scoring functions derived on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes.

Fleckenstein et al (Eur. J. Biochem., 240, 71-77, 1996) teaches method for determining peptides with modulated immunogenecity (i.e., with altered binding to leucocyte antigens to MHC molecules). Peptide libraries of undecapeptides with substitutions at variable positions are prepared synthetically, and binding of the peptides to human leukocyte antigen DRB1 is used as a "immunogenecity filter" to determine variant peptide immunogenecity. Abrams teaches that to modify MHC binding reactivity of peptides, rational targeted substitution of amino acid residues can be introduced to peptide ligands for regulation of immunogenic responses (p. 89). The referenced methods differs from the claimed invention in that both generation of variants and their testing are done in experimental conditions, not *in silico*.

There are numerous publications describing use of computerized algorithms to predict binding of peptides to MHC molecules. See, for example references of Altuvia et al or Meister et al or Buus et al, cited by applicants. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to substitute experimental determination of the immunogenecity of the candidate variant peptides with computerized estimates of their immunogenecity, such as described in Altuvia et al or Meister et al or Buus et al.

Further, in regard to method of generating of candidate peptides, computerized way of generating peptide in the claimed method does not render the referenced

methods utilizing chemical preparation of the peptides. Alternatively, computerized methods of generating peptide libraries with substitutions at variable positions proved to be an efficient way of modeling peptides which are further assessed for their biological functions. See for example, Mayo et al (WO 98/47089) or Mayo et al (US Patent 6,269,312).

Response to arguments

In regard to the rejection under 35 U.S.C. 103(a), applicant argues, first, that there is no suggestion of modifying immunogenecity *in silico* (as opposed to experimental protein modification), and there is no motivation to use computational filter. Examiner disagrees. All that is meant by "immunogenecity filter" is any scoring related to binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes (specification, p. 30), can be any of scoring functions derived on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes. Abrams teaches that rational targeted substitution of amino acid residues can be introduced to peptide ligands to modify MHC binding reactivity of the ligands and regulate immunogenic responses (p. 89). Thus, the Abrams reference does suggest that targeted generation of variant amino acid sequences (i.e., as in step (b) of claim 1) is desirable to obtain candidate peptides with modified MHC binding reactivity and immunogenicity. Further, in regard

to motivation to use computational filter, the secondary references used in the rejection do suggest computerized algorithms predicting binding of peptides to MHC molecules. Thus, Buus et al teach that computational methods, especially artificial neural networks should be able to recognize peptide patterns associated with MHC binding (see p. 212, first paragraph). Altuvia et al teach computer algorithm that predicts MHC binding by considering contribution of different amino acid substitutions to MHC binding grove. (See abstract, p. 2, last paragraph). Meister et al describe computer-based algorithms for T-cell epitope prediction bey searching peptide sequences for regions that contain MHC-binding motifs. Furthermore, Brusik et al (another reference submitted by applicants) cites minimizing of experimental efforts and facilitation of identification of potential T cell epitopes as motivation for use of *in silico* MHC binding prediction methods. Taken together, Examiner maintains that it would be *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to substitute experimental determination of the immunogenecity of the candidate variant peptides with computerized estimates of their immunogenecity, such as described in Altuvia et al or Meister et al or Buus et al.

Conclusion.

5. No claims are allowed

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

September 15, 2003

mlb

MICHAEL BORIN, PH.D
PRIMARY EXAMINER